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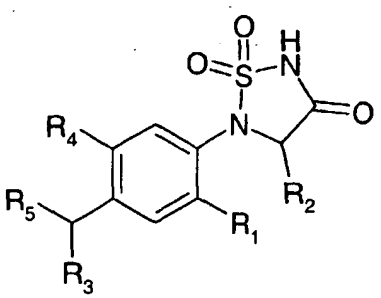
(54) Title: 1, 2, 5-THIADIAZOLIDIN-3-ONE 1, 1 DIOXIDE DERIVATIVES AS INHIBITORS OF PROTEIN TYROSINE PHOSPHATASE PTP1B



(I)

(57) Abstract: The invention concerns compounds of the formula (I) or pharmaceutically acceptable salts thereof wherein R_1, R_2, R_3, R_4, and R_5 have any of the meanings defined in the description. Processes for the manufacture of compounds of formula (I), compositions containing them, their use as inhibitors of protein tyrosine phosphatase PTP1B and their use for the treatment of diabetes mellitus are also described.

1,2,5-THIADIAZOLIDIN-3-ONE 1,1 DIOXIDE DERIVATIVES AS INHIBITORS OF PROTEIN TYROSINE PHOSPHATASE PTP1B

This invention relates to chemical compounds, or pharmaceutically acceptable salts thereof, more particularly to certain substituted thiadiazolidines or pharmaceutically acceptable salts thereof, which inhibit protein tyrosine phosphatase PTP1B and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use as therapeutic agents.

Protein phosphorylation is a post-translational event, which is responsible for the regulation of most cell signalling pathways. This phosphorylation is regulated by enzymes which either act to phosphorylate (protein kinases) or dephosphorylate (protein phosphatases) proteins. Protein phosphatases are divided into two major groups, i.e. those that dephosphorylate proteins which contain phosphorylated serine or threonine residues (Ser/Thr phosphatases) and those that dephosphorylate proteins which contain phosphorylated tyrosine residues (protein tyrosine phosphatases or PTPases). Unlike the protein kinase family, there is no sequence identity between these two groups of phosphatases. The PTPases are a large family of enzymes, which all contain the PTP signature motif in a highly conserved region of approximately 250 amino acids that make up the catalytic domain. The invariant cysteine residue has been shown to be critical to PTPase activity (reviewed by Cheng et al, Eur.J.Biochem. 269:1050-1059 (2002)).

The PTPases can be subdivided into three different classes, namely classical tyrosine specific PTPases; dual specific PTPases and low molecular weight PTPases. The classical tyrosine specific PTPases can be further subdivided into two groups: (i) receptor-type PTPases, which include CD45 and LAR, and which consist of an extracellular domain, a single transmembrane domain and most have two tandem repeated cytoplasmic PTP domains (although generally only one is active); and (ii) intracellular PTPases, which include PTP1B, TC-PTP and FAP, and which contain a single catalytic domain. The numerous amino and/or carboxyl domains may be involved in the subcellular localisation or regulatory function of these intracellular PTPases.

Initial analysis of the data generated from the human genome project has identified approximately 120 human protein phosphatases and a role for members of this family of proteins in disease is becoming clearer. Of the total, there are 42 PTPases, which have the potential to act as both positive and negative regulators of cell signalling. A number of these

PTPases have been shown to play a vital role in the regulation of cell signalling pathways associated with metabolism, growth, proliferation and differentiation, such that abnormal regulation may lead to a number of important disease states including diabetes and cancers (reviewed by Zhang, Annu. Rev. Pharmacol. Toxicol. 42:209-234 (2002)).

Insulin plays a key role in the control of blood glucose and defects in its synthesis or signalling lead to insulin resistance, diabetes and its associated complications. The glucose lowering and other effects of insulin are a consequence of insulin binding to its receptor and the subsequent activation of a number of downstream signalling cascades. Phosphorylation of tyrosine residues in a number of proteins in the insulin signalling cascade is critical to this signalling process. The insulin receptor is a tyrosine kinase that is autophosphorylated on tyrosine residues following activation by insulin. The phosphorylated insulin receptor catalyses the phosphorylation of its downstream substrates, including the insulin receptor substrates (IRSs). Removal of insulin itself is not sufficient to "switch off" these insulin sensitive signalling cascades. Dissociation of insulin is followed by dephosphorylation of the insulin receptor and of other components of the signalling cascade. A number of PTPases have been implicated to dephosphorylate proteins essential to this pathway, and as such are termed as negative regulators of insulin signalling (reviewed by Johnson et al, Nature Reviews Drug Discovery 1:696-709 (2002)).

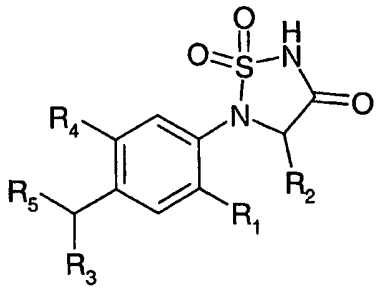
PTP1B was the first PTP to be purified to homogeneity. It was purified from human placenta, cloned and subsequently identified as a PTPase, shortly afterwards. Data generated in vitro, using a tri-phosphorylated peptide corresponding to the catalytic region of the insulin receptor kinase domain, showed that the activity of this peptide could be inhibited following dephosphorylation with PTP1B. Experiments involving cells in culture using antibodies, and antisense oligonucleotides suggested PTP1B to act as a negative regulator of insulin signalling (Ostman and Bohmer TRENDS in Cell Biology 11(6): 258-266 (2001)). Generation of PTP1B null mice further supported this hypothesis (Elchebly et al, Science 283:1544-1548 (1999)). PTP1B null mice are phenotypically normal with a normal lifespan, as compared to their wild type littermates. However, PTP1B null mice demonstrate tissue specific up-regulation of the insulin receptor (in liver and muscle) and improved insulin sensitivity as demonstrated using an oral glucose tolerance test. Surprisingly, as well as having improved insulin sensitivity, the PTP1B null mice are resistant to diet induced obesity (DIO). This resistance to DIO may suggest that PTP1B has a role in the central regulation of energy balance and work is on going to try to understand further this mechanism. PTP1B has

been shown to be present in the hypothalamus and recent data has suggested that JAK2 is another substrate for PTP1B (Cheng et al, Dev. Cell 2:497-503 (2002). Leptin, a satiety hormone released from the adipocytes, binds to the leptin receptor and induces JAK2 phosphorylation. As with the insulin receptor, JAK2 has a number of substrates. It is thought that PTP1B dephosphorylation of JAK2 may result in changes to the subsequent downstream signalling cascade and may be responsible, at least in part, for the resistance to DIO, in the PTP1B null mice. Accordingly evidence suggests that PTP1B inhibitors are of benefit in the treatment of type 1 or type 2 diabetes, obesity and other conditions which may result from the abnormal regulation of tyrosine phosphatase PTP1B, such as metabolic syndrome (syndrome X), hyperglycemia, hyperinsulinemia, dyslipidemia, polycystic ovarian disease, hypertension, cardiovascular disease (Ukkola and Santaniemi, Journal of Internal Medicine 251:467-475 (2002)).

Compounds which modulate the activity of PTPases are disclosed in International Patent Application, publication number WO 97/40017.

Accordingly there is a continuing need to identify novel compounds which are PTP1B inhibitors. We have found that the compounds defined in the present invention, or pharmaceutically acceptable salts thereof, have surprisingly effective PTP1B inhibitory properties, and accordingly have value in the treatment of disease states mediated by this enzyme.

Accordingly there is provided a compound of formula (I):



(I)

wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy,

heteroaryloxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_6)_m-X-NR_7R_8$ wherein

m is 1, 2 or 3;

R_6 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $-S(O)_2-$; and R_7 and R_8 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_7 and R_8 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_7 is hydrogen, (1-6C)alkyl or aryl, and R_8 is $-COR_9$ or SO_2R_9 wherein R_9 is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is selected from H, (1-6C)alkyl, halogeno, halogeno(1-6C)alkyl and (1-6C)alkoxy;

R_3 is $-NHR_{10}$ wherein R_{10} is $-C(O)R_{11}$, and R_{11} is $-(CHR_{12})_n-R_{13}$; or R_3 is $-(CHR_{14})_p-R_{15}$ wherein R_{14} is hydrogen or (1-6C)alkyl and

R_{15} is (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, cyano, carbamoyl or -CONH-$(CHR_{12})_n$-R_{13}; or R_{15} is -NHR_{10} wherein R_{10} is as defined above; or R_{15} is –$(CHR_{16})_q$-CONH-$(CHR_{12})_n$-R_{13} wherein R_{16} is amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, carbamoyl, -CONH-$(CHR_{12})_n$-R_{13} or -NHR_{10} wherein R_{10} is as defined above; and wherein n is the integer 1, 2 or 3; p is zero or the integer 1,2 or 3; q is the integer 1, 2 or 3; and R_{12}, R_{13} and R_{16} are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkyl, hydroxy, hydroxy(1-6C)alkyl, (1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkyl, (1-6C)alkylsulfonyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkylsulfinyl, (1-6C)alkylsulfinyl(1-6C)alkyl, aryl, aryloxy, aryl(1-6C)alkyl, heteroaryl, heteroaryloxy, heteroaryl(1-6C)alkyl, amino, amino(1-6C)alkyl, carboxy, carboxy(1-4C)alkyl, carbamoyl, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino, (2-6C)alkanoylamino(1-6C)alkyl, sulfamoyl and sulfamoyl(1-6C)alkyl; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_4 is hydrogen, (1-6C)alkyl, aryl or heteroaryl;

R_5 is hydrogen or (1-6C)alkyl;

and wherein any aryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be

the same or different; or two adjacent carbons of said aryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention is provided a compound of the formula (I) wherein R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_6)_m-X-NR_7R_8$ wherein

m is 1, 2 or 3;

R_6 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $-S(O)_2-$; and R_7 and R_8 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_7 and R_8 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_7 is hydrogen, (1-6C)alkyl or aryl, and R_8 is $-COR_9$ or SO_2R_9 wherein R_9 is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is H or (1-6C)alkyl;

R_3 is -NHR_{10} wherein R_{10} is –$C(O)R_{11}$, and R_{11} is -$(CHR_{12})_n$-R_{13}; or R_3 is -$(CHR_{14})_p$-R_{15} wherein R_{14} is hydrogen or (1-6C)alkyl and

R_{15} is (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, cyano, carbamoyl or -CONH-$(CHR_{12})_n$-R_{13}; or R_{15} is -NHR_{10} wherein R_{10} is as defined above; or R_{15} is –$(CHR_{16})_q$-CONH-$(CHR_{12})_n$-R_{13} wherein R_{16} is amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, carbamoyl, -CONH-$(CHR_{12})_n$-R_{13} or -NHR_{10} wherein R_{10} is as defined above; and wherein n is the integer 1, 2 or 3; p is zero or the integer 1,2 or 3; q is the integer 1, 2 or 3; and R_{12}, R_{13} and R_{16} are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkyl, hydroxy, hydroxy(1-6C)alkyl, (1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkyl, (1-6C)alkylsulfonyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkylsulfinyl, (1-6C)alkylsulfinyl(1-6C)alkyl, aryl, aryloxy, aryl(1-6C)alkyl, heteroaryl, heteroaryloxy, heteroaryl(1-6C)alkyl, amino, amino(1-6C)alkyl, carboxy, carboxy(1-4C)alkyl, carbamoyl, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino, (2-6C)alkanoylamino(1-6C)alkyl, sulfamoyl and sulfamoyl(1-6C)alkyl; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_4 is hydrogen, (1-6C)alkyl, aryl or heteroaryl;

R_5 is hydrogen or (1-6C)alkyl;

and wherein any aryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy,

heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;

or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and *tert*-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy. Where halogenoalkyl is referred to, this includes mono-, di-, tri- and per-halogenoalkyl. An analogous convention applies to halogenoalkoxy and halogenoalkylthio.

It is to be understood that, insofar as certain of the compounds of Formula **(I)** defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

A suitable value for aryl, or for aryl which is part of a value defined herein for R_1 to R_{16} is, for example, a totally unsaturated, mono or bicyclic carbon ring that contains 6-12 atoms. Suitable values for aryl include phenyl or naphthyl, particularly phenyl.

A suitable value for heteroaryl, or for heteroaryl which is part of a value defined herein for R_1 to R_{16} is, for example, a totally unsaturated mono or bicyclic ring containing 5-12 atomes of which at least one atom is chosen from oxygen, sulphur and nitrogen. For

example an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

Suitable values for R_1 to R_{16} or for groups which are part of a value defined herein for R_1 to R_{16}, or for substituents on an aryl or heteroaryl group, include :-

for (1-6C)alkyl:	(1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl and *tert*-butyl;
for (1-6C)alkoxy:	(1-4C)alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (1-6C)alkylthio:	(1-4C)alkylthio, such as methylthio, ethylthio and propylthio;
for halogeno	fluoro, chloro, bromo and iodo;
for halogeno-(1-6C)alkyl:	halogeno(1-4C)alkyl, such as chloromethyl, 2-chloroethyl, 1-chloroethyl, 3-chloropropyl, fluoromethyl and difluoromethyl;
for halogeno-(1-6C)alkoxy:	halogeno(1-4C)alkoxy, such as chloromethoxy, 2-chloroethoxy, 1-chloroethoxy, 3-chloropropoxy, trifluoromethoxy and 2,2,2-trifluoroethoxy;
for halogeno-(1-6C)alkylthio:	halogeno(1-4C)alkylthio, such as chloromethylthio, 2-chloroethylthio, 1-chloroethylthio and 3-chloropropylthio;
for hydroxy-(1-6C)alkoxy:	hydroxy(1-4C)alkoxy, such as 2-hydroxyethoxy and 3-hydroxypropoxy;
for dihydroxy-(1-6C)alkoxy:	dihydroxy(1-4C)alkoxy, such as 2,3-dihydroxypropoxy;

for (1-6C)alkoxy(1-6C)alkoxy:	(1-4C)alkoxy(1-4C)alkoxy, such as methoxymethoxy, 2-methoxyethoxy, ethoxymethoxy and 2-(ethoxy)ethoxy;
for aryl(1-6C)alkoxy:	aryl(1-4C)alkoxy, such as benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, 3-(1-naphthyl)propoxy and 3-(2-naphthyl)propoxy
for aryloxy(1-6C)alkoxy:	aryloxy(1-4C)alkoxy, such as phenoxymethoxy, phenoxyethoxy, phenoxypropoxy, 1-naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, 3-(1-naphthyl)propoxy and 2-(2-naphthyl)propoxy;
for (1-6C)alkoxy-(1-6C)alkylthio:	(1-4C)alkoxy(1-4C)alkylthio, such as methoxymethylthio, ethoxymethylthio, 1-methoxyethylthio, 2-methoxyethylthio, 2-ethoxyethylthio and 3-methoxypropylthio;
(1-6C)alkylthio(1-6C)alkoxy:	(1-4C)alkylthio(1-4C)alkoxy, such as methylthiomethoxy, 2-(methylthio)ethoxy, ethylthiomethoxy and 2-(ethylthio)ethoxy;
(1-6C)alkylsulfinyl(1-6C)alkoxy:	(1-4C)alkylsulfinyl(1-4C)alkoxy, such as methylsulfinylmethoxy, 2-(methylsulfinyl)ethoxy, ethylsulfinylmethoxy and 2-(ethylsulfinyl)ethoxy;
(1-6C)alkylsulfonyl(1-6C)alkoxy	methylsulfonylmethoxy, 2-(methylsulfonyl)ethoxy, ethylsulfonylmethoxy and 2-(ethylsulfonyl)ethoxy;
for aryl(1-6C)alkylthio:	aryl(1-4C)alkylthio, such as phenylmethylthio, 2-phenylethylthio, 3-phenylpropylthio, 1-naphthylmethylthio and 2-naphthylmethylthio;
for aryloxy(1-6C)alkylthio:	aryloxy(1-4C)alkylthio, such as phenoxymethylthio, 2-phenoxyethylthio, 3-phenoxypropylthio, 1-naphthyloxymethylthio and 2-naphthyloxymethylthio;

for (1-6C)alkoxy-(1-6C)alkyl:	(1-4C)alkoxy(1-4C)alkyl, such as methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for aryloxy(1-6C)alkyl:	aryloxy(1-4C)alkyl, such as phenoxymethyl, 1-phenoxyethyl, 2-phenoxyethyl and 3-phenoxypropyl;
for (1-6C)alkylthio(1-6C)alkyl:	(1-4C)alkylthio(1-4C)alkyl, such as methylthiomethyl, 2-(methylthio)ethyl, ethylthiomethyl and 2-(ethylthio)ethyl;
for arylthio(1-6C)alkyl:	arylthio(1-4C)alkyl, such as phenylthiomethyl, 1-phenylthioethyl, 2-phenylthioethyl and 3-phenylthiopropyl;
for (1-6C)alkylsulfinyl(1-6C)alkyl:	(1-4C)alkylsulfinyl(1-4C)alkyl, such as methylsulfinylmethyl, 2-(methylsulfinyl)ethyl
for arylsulfinyl(1-6C)alkyl:	arylsulfinyl(1-4C)alkyl, such as phenylsulfinylmethyl, 2-(phenylsulfinyl)ethyl, 1-naphthylsulfinylmethyl, 2-(1-naphthylsulfinyl)ethyl;
for (1-6C)alkylsulfonyl(1-6C)alkyl:	(1-4C)alkylsulfonyl(1-4C)alkyl, such as methylsulfonylmethyl, 2-(methylsulfonyl)ethyl
for arylsulfonyl(1-6C)alkyl:	arylsulfonyl(1-4C)alkyl, such as phenylsulfonylmethyl, 2-(phenylsulfonyl)ethyl
	carbamoyl(1-6C)alkoxy: carbamoylmethoxy, 2-(carbamoyl)ethoxy, 3-(carbamoyl)propoxy
carbamoyl(1-6C)alkyl:	carbamoyl(1-4C)alkyl, such as carbamoylmethyl, 2-(carbamoyl)ethyl, 3-(carbamoyl)propyl
carbamoyl(1-6C)alkoxy:	carbamoyl(1-4C)alkoxy, such as carbamoylmethoxy, 2-(carbamoyl)ethoxy, 3-(carbamoyl)propoxy
(2-6C)alkanoylamino(1-6C)alkoxy:	(2-4C)alkanoylamino(1-6C)alkoxy, such as acetamidomethoxy, propionamidomethoxy and 2-acetamidoethoxy;

for (2-6C)alkanoylamino-(1-6C)alkyl:	(2-4C)alkanoylamino(1-4C)lkyl, such as acetamidomethyl, propionamidomethyl and 2-acetamidoethyl;
for aryl(1-6C)alkyl:	aryl(1-4C)alkyl, such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 3-(1-naphthyl)propyl and 3-(2-naphthyl)propyl;
for hydroxy(1-6C)alkyl:	hydroxy(1-4C)alkyl, such as hydroxymethyl, 2-hydroxyethyl and 3-hydroxypropyl;
for dihydroxy(2-6C)alkyl:	dihydroxy(2-4C)alkyl, such as 1,2-dihydroxyethyl and 1,3-dihydroxypropyl;
for amino(1-6C)alkyl:	amino(1-4C)alkyl, such as aminomethyl, 2-aminoethyl and 3-aminopropyl;
for carboxy(1-6C)alkyl:	carboxy(1-4C)alkyl, such as carboxymethyl, 2-carboxyethyl and 3-carboxypropyl;
for sulfamoyl(1-6C)alkyl:	sulfamoyl(1-4C)alkyl, such as sulfamoylmethyl, 2-sulfamoylethyl and 3-sulfamoylpropyl;
for (2-8C)alkenyl:	(2-6C)alkenyl, such as vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	(2-6C)alkynyl, such as ethynyl, 2-propynyl and but-2-ynyl;
for (2-6C)alkenyloxy:	(2-4C)alkenyloxy, such as vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	(2-4C)alkynyloxy, such as ethynyloxy and 2-propynyloxy;
for (1-6C)alkylsulfinyl:	(1-4C)alkylsulfinyl, such as methylsulfinyl and ethylsulfinyl;
for (1-6C)alkylsulfonyl:	(1-4C)alkylsulfonyl, such as methylsulfonyl and ethylsulfonyl;
for (1-6C)alkylamino:	(1-4C)alkylamino, such as methylamino, ethylamino, propylamino, isopropylamino and butylamino;

for di-[(1-6C)alkyl]amino:	di-[(1-4C)alkyl]amino, such as dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	(1-4C)alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and *tert*-butoxycarbonyl;
for *N*-(1-6C)alkylcarbamoyl:	*N*-(1-4C)alkylcarbamoyl, such as *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl;
for *N*,*N*-di-[(1-6C)alkyl]carbamoyl:	*N*,*N*-di-[(1-4C)alkyl]carbamoyl, such as *N*,*N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N*,*N*-diethylcarbamoyl;
for (2-6C)alkanoyl:	(2-4C)alkanoyl, such as acetyl and propionyl;
for (2-6C)alkanoyloxy:	(2-4C)alkanoyloxy, such as acetoxy and propionyloxy;
for (2-6C)alkanoylamino:	(2-4C)alkanoylamino, such as acetamido and propionamido;
for *N*-(1-6C)alkyl-(2-6C)alkanoylamino:	*N*-(1-4C)alkyl-(2-4C)alkanoylamino, such as *N*-methylacetamido and *N*-methylpropionamido;
for *N*-(1-6C)alkylsulfamoyl:	*N*-(1-4C)alkylsulfamoyl, such as *N*-methylsulfamoyl and *N*-ethylsulphamoyl;
for *N*,*N*-di-[(1-6C)alkyl]sulfamoyl:	*N*,*N*-di-[(1-4C)alkyl]sulfamoyl, such as *N*,*N*-dimethylsulfamoyl;
for (1-6C)alkanesulfonylamino:	(1-4C)alkanesulfonylamino, such as methanesulfonylamino and ethanesulfonylamino;
for *N*-(1-6C)alkyl-(1-6C)alkanesulfonylamino:	*N*-(1-4C)alkyl-(1-4C)alkanesulfonylamino, such as *N*-methylmethanesulfonylamino and *N*-methylethanesulfonylamino;
for sulfamoyl(1-6C)alkyl:	sulfamoyl(1-4C)alkyl such as sulfamoylmethyl, 2-sulfamoylethyl and 3-sulfamoylpropyl.

A suitable value for a diradical of formula $-O(CH_2)_{1-4}O-$ includes, for example,

methylenedioxy and ethylenedioxy.

A suitable value for R_7 and R_8 when, together with the nitrogen atom to which they are attached, they form a heterocyclic ring includes, for example, a saturated or partially saturated heterocyclic ring optionally substituted with a (1-6C)alkyl group, such as pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or *N*-methylpiperazino.

Suitable values for optional substituents on an aryl or heteroaryl moiety of an aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy or heteroaryloxy substituent include, for example, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulfamoyl, *N*,*N*-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulfonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy and hydroxy(1-6C)alkyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess PTP1B inhibitory activity.

It is also to be understood that certain compounds of the formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess PTP1B inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

(1) R_1 is hydrogen

(2) R_1 has any of the values defined herein other than hydrogen

(3) R_1 is $-Z-(CHR_7)_m-X-NR_8R_9$

(3) R_1 is (1-6C)alkoxy, such as (1-4C)alkoxy, for example methoxy

(4) R_1 is hydroxy-(1-6C)alkoxy, such as hydroxy(1-4C)alkoxy, for example, 2-hydroxyethoxy

(5) R_1 is (1-6C)alkoxy(1-6C)alkoxy, such as (1-4C)alkoxy(1-4C)alkoxy, for example. 2-methoxyethoxy

(6) R_1 is (1-6C)alkylthio(1-6C)alkoxy, such as (1-4C)alkylthio(1-4C)alkoxy, for example, 2-(methylthio)ethoxy

(7) R_1 is (1-6C)alkylsulfinyl(1-6C)alkoxy, such as (1-4C)alkylsulfinyl(1-4C)alkoxy, for example, 2-(methylsulfinyl)ethoxy

(8) R_1 is (1-6C)alkylsulfonyl(1-6C)alkoxy, such as (1-4C)alkylsulfonyl(1-4C)alkoxy, for example, 2-(methylsulfonyl)ethoxy

(9) R_1 is aryl(1-6C)alkoxy, such as aryl(1-4C)alkoxy, for example, benzyloxy or phenethyloxy

(10) R_1 is fluoro(1-6C)alkoxy, such as fluoro(1-4C)alkoxy, for example trifluoromethoxy or 2,2,2-trifluoroethoxy

(11) R_1 is carbamoyl(1-6C)alkoxy, such as carbamoyl(1-4C)alkoxy, for example, carbamoylmethoxy or 2-carbamoylethoxy

(12) R_1 is (2-6C)alkanoylamino(1-6C)alkoxy, such as (2-4C)alkanoylamino(1-4C)alkoxy, for example, acetamidomethyl

(13) R_1 is (1-6C)alkoxy-(1-6C)alkyl, such as (1-4C)alkoxy-(1-4C)alkyl, for example, 2-methoxyethyl

(14) R_1 is aryloxy(1-6C)alkyl, such as aryloxy(1-4C)alkyl, for example, phenyloxymethyl or 2-(phenyloxy)ethyl

(15) R_1 is (1-6C)alkylsulfinyl(1-6C)alkyl, such as (1-4C)alkylsulfinyl(1-4C)alkyl, for example, methylsulfinylmethyl or 2-(methylsulfinyl)ethyl

(16) R_1 is (1-6C)alkylsulfonyl(1-6C)alkyl, such as (1-4C)alkylsulfonyl(1-4C)alkyl, for example, methylsulfonylmethyl or 2-(methylsulfonyl)ethyl

(17) R_1 is (2-6C)alkanoylamino(1-6C)alkyl, such as (2-4C)alkanoylamino(1-4C)alkyl, for example, acetylaminomethyl or 2-(acetylamino)ethyl

(18) R_1 is carbamoyl(1-6C)alkyl, such as carbamoyl(1-4C)alkyl, for example, carbamoylmethyl or 2-carbamoylethyl

(19) R_2 is hydrogen

(20) R_3 is $-NH-CO-R_{11}$

(21) R_3 is $-NH-CO-R_{11}$ wherein R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} and R_{13} are independently selected from hydrogen and (1-4C)alkyl and n is 1, 2 or 3

(22) R_3 is $-NH-CO-R_{11}$ wherein R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} is hydrogen, R_{13} is aryl or aryl(1-6C)alkyl, and n is 1, 2 or 3

(23) R_3 is $-(CHR_{14})_p-NH-CO-R_{11}$ wherein p is 0 or 1, R_{14} is hydrogen, and R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} and R_{13} are independently selected from hydrogen and (1-4C)alkyl and n is 1, 2 or 3

(24) R_3 is $-(CHR_{14})_p-(CHR_{16})_q-CO-NH-(CHR_{12})_n-R_{13}$ wherein p is zero, q is 1; R_{16} is $-NH-CO-(CHR_{12})_n-R_{13}$; n is 1; R_{12} and R_{13} are independently selected from hydrogen or (1-4C)alkyl

(25) R_3 is $-(CHR_{14})_p-R_{15}$ wherein p is 1, R_{14} is hydrogen, and R_{15} is $-CONH-(CHR_{12})_n-R_{13}$ in which R_{12} and R_{13} are independently selected from hydrogen and (1-4C)alkyl

(26) R_4 is hydrogen

(27) R_5 is hydrogen

(28) R_6 is hydrogen

(29) R_7 is hydrogen

(30) R_8 is hydrogen

(31) R_8 is (1-4C)alkyl

(32) R_9 is $-C(O)$(1-4C)alkyl

(33) R_9 is $-S(O)_2$(1-4C)alkyl

(34) X is $-C(O)-$

(35) m is the integer 1

(36) m is the integer 2

(37) m is the integer 3

(38) Z is a covalent bond

(39) Z is –O-

(40) R_{10} is $-C(O)R_{11}$

(41) R_{12} is hydrogen, (1-4C)alkyl or (1-4C)alkoxy

(42) R_{13} is (1-4C)alkoxy, hydroxy, aryl, heteroaryl, (1-4C)alkylsulfonyl(1-4C)alkyl or (1-4C)alkylsulfinyl(1-4C)alkyl

(43) n is the integer 1

(44) n is the integer 2

(45) n is the integer 3

(46) R_{14} is hydrogen

(47) R_{15} is $-(CHR_{16})_q$-CONH-$(CHR_{12})_n$-R_{13}

(48) R_{16} is hydrogen, (1-4C)alkyl or (1-4C)alkoxy

(49) p is zero

(50) p is the integer 1

(51) p is the integer 2

(52) p is the integer 3

(53) q is the integer 1

(54) q is the integer 2

(55) q is the integer 3

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, (1-6C)alkylthio, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy; and R_2, R_3, R_4 and R_5 have any of the values defined herein. Within this group of compounds, a further aspect of the invention comprises a compound of the formula I wherein R_1 is unsubstituted (1-6C)alkoxy or a substituted (1-6C)alkoxy group included in the group above, and particularly unsubstituted (1-6C)alkoxy, such as methoxy.

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, (1-6C)alkylthio, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy; and R_2, R_3, R_4 and R_5 have any of the values defined herein. Within this group of compounds, a further aspect of the invention comprises a compound of the formula I wherein R_1 is unsubstituted (1-6C)alkoxy or a substituted (1-6C)alkoxy group included in the group above, and particularly unsubstituted (1-6C)alkoxy, such as methoxy.

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 has any of the values defined herein; R_2, R_4 and R_5 are each hydrogen; and R_3 is $-(CHR_{14})_p$-NH-CO-R_{11} wherein p is 0 or 1; R_{14} is hydrogen; and R_{11} has any of the values defined herein, for example those values for R_{11} given in (21), (22) and (23) above Within these compounds of the invention, a particular group of compounds of interest are those in which p is 0.

In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined herein, wherein R_1, R_2, R_4 and R_5 are each hydrogen; and R_3 is $-(CHR_{14})_p$-NH-CO-R_{11} wherein p is 0 or 1; R_{14} is hydrogen; and R_{11} has any of the values defined herein, for example those values for R_{11} given in (21), (22) and (23) above. Within these compounds of the invention, a particular group of compounds of interest are those in which p is 0.

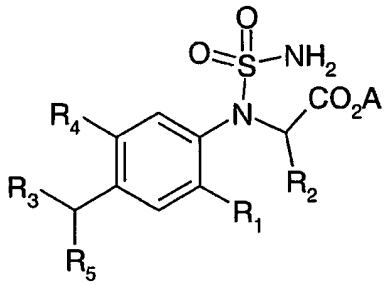
In another aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, wherein R_1 is (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkanoylamino(1-6C)alkyl, carbamoyl(1-6C)alkyl; R_2, R_4 and R_5 are each hydrogen; R_3 is $-(CHR_{14})_p$-NH-CO-R_{11} wherein p is 0 or 1; R_{14} is hydrogen; and R_{11} has any of the values

defined herein, for example those values for R_{11} given in (21), (22) and (23) above; or a pharmaceutically acceptable salt thereof. Within this group of compounds, a further aspect of the invention comprises a compound of the formula I wherein R_1 is unsubstituted (1-6C)alkoxy or a substituted (1-6C)alkoxy group included in the group above, and particularly unsubstituted (1-6C)alkoxy, such as methoxy.

In another aspect of the invention, compounds of the invention are any one of the Examples, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula **(I)**) comprises of:

(a) cyclisation of a compound of formula **(II)**:



(II)

wherein A is a (1-6C)alkyl, aryl or aryl(1-6C)alkyl group, for example methyl, ethyl, phenyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin; and thereafter if necessary or desirable:

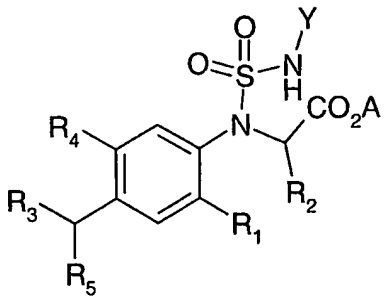
i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt thereof.

The cyclisation may be carried out using a base, such as sodium hydride or piperidine. The reaction is generally carried out in an inert solvent or diluent, such as tetrahydrofuran, at or about ambient temperature.

Compounds of the formula **(II)** may be prepared by deprotection of a compound of the formula **(III)**

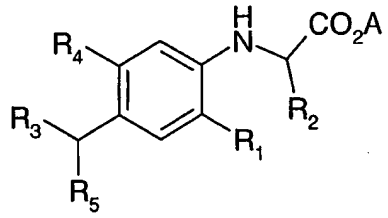


(III)

wherein Y is a protecting group, for example a *tert*-butoxycarbonyl or 9-fluorenylmethoxycarbonyl group.

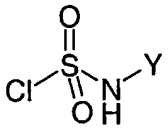
A *tert*-butoxycarbonyl protecting group may be removed under acidic conditions, for example using aqueous trifluoroacetic acid at ambient temperature. A 9-fluorenylmethoxycarbonyl protecting group may be removed using basic conditions, for example using piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene. When basic conditions are used to remove the protecting group, concomitant cyclisation to a compound of formula (I) may occur.

A compound of the formula (III) may be prepared by sulphamoylation of a compound of the formula (IV)



(IV)

with a sulphamoylating agent of formula (V)

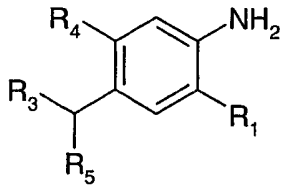


(V)

wherein Y is a protecting group, for example *tert*-butoxycarbonyl or 9-fluorenylmethoxycarbonyl. Compounds of the formula (V) may be obtained using the methods described by Dewynter in Tetrahedron, 1993, Vol. 49, page 72. The sulphamoylation reaction is generally carried out in the presence of a base, such as triethylamine, in an inert solvent or diluent such as dichloromethane, under an inert

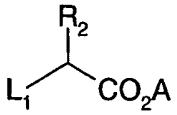
atmosphere, such as argon or nitrogen, and at a temperature in the range -10°C to ambient temperature, for example at about 0°C.

A compound of the formula (IV) may be prepared by reaction of a compound of the formula (VI)



(VI)

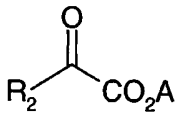
with an alkylating agent of the formula (VII)



(VII)

wherein L_1 is a displaceable group, for example chloro, bromo, iodo, tosyloxy, mesyloxy or trifluoromethanesulfonyloxy, and A is (1-6C)alkyl, aryl or aryl(1-6C)alkyl, for example methyl, ethyl, phenyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin. The alkylation is carried out using procedures well known in the art for alkylation of anilines or as described herein, or by analogy therewith.

Alternatively a compound of the formula (IV) may be prepared by reaction of a compound of the formula (VI) with an aldehyde or ketone of formula (VIII)



(VIII)

wherein A and R_2 are as previously defined, in the presence of a reducing agent, for example sodium cyanoborohydride. Compounds of the formula VI are commercially available or may be obtained using procedures well known in the art, or by analogy therewith.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of

the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group

for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A further aspect of the invention comprises novel intermediates used in the manufacture of the compounds of formula I.

As stated hereinbefore the compounds defined in the present invention possess PTP1B inhibitory activity. These properties may be assessed using the following assay.

Assay

Expression and purification of human PTP1B

A T7 based expression vector encoding residues 1-321 of human PTP1B was transformed into Escherichia coli K12 host strain DS 410 (DE3). A 600ml seeder of the recombinant was grown in Luria-Bertani medium containing 10μg/ml tetracycline at 37°C for 14 hours to an optical density of 5 at 550nm (which may be expressed as $OD_{550} = 5$) on an orbital shaker with a 2" throw at 250rpm. This was then used to inoculate a 20/l fermenter (Braun U30D). The bacteria were grown at 37°C in high yeast extract (HYE) 20 medium containing 3.0g/l KH_2PO_4, 6.0g/l Na_2HPO_4, 0.5g/l NaCl, 2.0g/l casein hydrolysate, 10.0g/l $(NH_4)_2SO_4$, 35.0g/l glycerol, 20.0g/l yeast extract, 0.5g/l $MgSO_4.7H_2O$, 0.0294g/l $CaCl_2.2H_2O$, 0.008g/l thiamine, 40mg/l $FeSO_4$, 20mg/l citric acid, 10ug/ml tetracycline, and trace elements, pH 6.7.

The cells were grown to OD_{550}=14 and induced by addition of isopropyl b-d-thiogalacto-pyranoside (IPTG) to a final concentration of 0.1mM. Cells were harvested after 4 hours induction when the OD_{550} = 42 by centrifugation at 3,500g for 30mins and stored at -80°C.

Frozen cell paste is taken, thawed and suspended (10g/ml) in lysis buffer (75mM 2-(*N*-morpholino)ethanesulfonic acid (MES), 1mM EDTA, 1mM DTT, pH6.3). The cells are lysed by two passages through an 'Emulsiflex C5' homogeniser (available from Glen-Creston, 16 Dalston Gardens, Stanmore, HA7 1DA, England) and the soluble fraction clarified by centrifugation (58,000g for 1 hour). The supernatant is passed over an 'SP-Sepharose' column (available from Amersham Biosciences UK Ltd, Amersham Place, Little Chalfont, Bucks, HP7 9NA, England) (typically 0.5ml - 1ml resin per gram of starting paste) pre-equilibrated in lysis buffer. After passaging the supernatant, the column is washed to baseline with 4 column volumes of lysis buffer. Bound proteins are eluted from the column with a 20 column volume 0mM to 500mM sodium chloride gradient. Fractions are collected and those containing PTP1B, as judged by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), are pooled and concentrated using an 'Amicon stirred cell' with a 10,000 molecular weight cut off membrane (available from Millipore (U.K.) Limited, Units 3&5, The Courtyards, Hatters Lane, Watford, WD18 8YH, England). The PTP1B pool is further purified by passing down a 'Superdex 75' (available from Amersham Biosciences UK Ltd) size exclusion column equilibrated in storage buffer(75mM MES, 100mM NaCl, 1mM dithiothreitol (DTT), 1mM ethylenediaminetetraacetic acid (EDTA), 30% glycerol. Fractions are collected and those containing the PTP1B are pooled and stored at –20 ^{O}C prior to use.

Measurement of PTP1B activity

Human PTP1B activity was measured using p-nitrophenol phosphate (pNPP) as a substrate in 384 well microtitre plates. The assay was conducted at room temperature with a final assay volume of 103µl/well.

Compounds were evaluated using a truncated form of PTP1B (corresponding to the first 314 amino acids) as described above. Compounds were prepared in dimethyl sulfoxide (DMSO) and transferred to column 1 of a 96 well microtitre plate. A 1:3 serial dilution of each compound in DMSO was carried out in across the plate.

For enzyme assays, 3µl compound was transferred to each row of a 384 well microtitre assay plate. Each compound was assayed in duplicate at each concentration. 75µl enzyme @

1.37μg/ml (1.37x final) in assay buffer (50mM (bis[2-hydroxyethyl]imino-tris[hydroxymethyl]methane) pH 7.0, 2mM EDTA, 5mM DTT, 0.001% t-octylphenoxypolyethoxyethanol) was to added to each well and the enzyme and compound mix, incubated for 10 minutes. The reaction was initiated by the addition of 25μl pNPP at 4.12x final. The compounds were assayed with pNPP either at Km (0.4mM final) or 10x Km (4mM final). Reactions were stopped 15 minutes after the addition of substrate, by the addition of 10ul 1M NaOH.

The enzyme activity was determined by measurement of the absorbance at 405nm. Each plate carried both DMSO vehicle controls (maximum signal) and enzyme buffer controls (minimum signal). Data was calculated with appropriate corrections for absorbance at 405nm of the compounds and pNPP.

Inhibition was expressed as IC_{50} values in μM.

Generally the compounds, when assayed with pNPP at Km (0.4mM final) or 10xKm (4mM final), gave IC_{50} values of 450 μM or less. Example 3 gave an IC_{50} value of 44μM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.1 – 50 mg/kg that normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective PTB1B inhibitors, and accordingly

have value in the treatment of disease states mediated by this enzyme. Such disease states may include, for example, any of those previously referred to herein.

According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man, and in particular for use in the treatment of diabetes mellitus.

Thus according to this aspect of the invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament, and more particularly for use as a medicament for producing a PTP1B inhibitory effect in a warm-blooded mammal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a PTP1B inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of diabetes mellitus.

According to a further feature of this aspect of the invention there is provided a method for producing a PTP1B inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method for treating diabetes mellitus in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of PTP1B in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of PTP1B described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances

and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with PTP1B inhibitors, particularly those of the present invention, may include other antidiabetic agents, such as sulfonylureas and other insulin secretagogues, PPAR γ agonists and other insulin sensitisers, biguanides, glucosidase inhibitors, SGLT2 inhibitors, PPAR α/γ dual agonists, aP2 inhibitors, glycogen phoshporylase inhibitors, glucokinase activators, advanced glycosylation end product inhibitors, meglitinides and insulin.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) temperatures are given in degrees Celsius (°C); operations were carried out under an atmosphere of an inert gas such as argon or nitrogen;
(ii) organic solutions were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 40°C;
(iii) Reverse phase HPLC (Prep LC) purification was carried out on a Waters ZQ Fractionlynx system where a Phenomenex column was used (Synergi Polar-RP, 4μ, 80Å, size 100 x 21.20mm); thin layer chromatography (TLC) was carried out on silica gel plates;
(iv) Example 2 was conveniently carried out using a 'Trident' automated library synthesizer (from Argonaut Technologies, 1101 Chess drive, Foster City, CA 94404, USA) under an inert atmosphere;
(v) in general, the course of reactions was followed by TLC and/or LC-MS and reaction times are given for illustration only;
(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development;

(vii) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm), determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) or perdeuteriochloroform ($CDCl_3$) as solvent;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(x) solvent ratios are given in volume : volume (v/v) terms;

(xi) mass spectra (MS) were run with LC-MS negative ion APCI mass spectrometry; values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is (M-H);

(xii) The following abbreviations are used:

DMF	dimethylformamide;
DIPEA	*N*,*N*-diisopropylethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid

Example 1

5-[4-(Acetamidomethyl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

A solution of ethyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-(aminosulphonyl)glycinate (1.38 g, 4.2 mmol) in THF (90 ml) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil; 840 mg, 21 mmol) in THF (9 ml) under argon over 30 minutes. The solution was stirred at ambient temperature for a further 1 hour. Water (50 ml) was added slowly and the mixture was then extracted with diethyl ether (50 ml). The aqueous phase was acidified with 2M HCl and extracted with ethyl acetate (3x50 ml). The combined ethyl acetate extracts were washed with water (30 ml), followed by brine (30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with ethyl acetate to give the title product (218 mg) as a pale yellow solid; ^{1}H NMR (DMSO-d6): 1.8(3H,s), 4.2(2H,d), 4.4(2H,s), 7.1 (2H,dd), 7.2 (2H,dd), 8.2(1H,br) : m/z 284 (M+H)

The starting material ethyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-(aminosulphonyl)glycinate was obtained as follows:-

(i) Ethyl bromoacetate (1.22 ml, 11.05 mmol) was added to a solution of *N*-(4-aminobenzyl)acetamide (1.91 g, 11.6 mmol) in DMF(10 ml) containing DIPEA (1.05 ml),

and the mixture was heated at 60°C overnight. After cooling to ambient temperature, the mixture was poured into ice water (50 ml) and extracted with ethyl acetate (3x50 ml). The combined ethyl acetate extracts were washed with water (30 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate/hexane to give ethyl *N*-{4-[(acetylamino)methyl]phenyl}glycinate (1.1 g); ^{1}H NMR ($CDCl_3$): 1.15(3H,t), 2.0(3H,s), 3.8(2H,s), 4.2-4.4(5H,m), 5.6(1H,br), 6.5(2H,d), 7.1(2H,d);

(ii) A 0.66 M solution of *tert*-butyl chlorosulfonylcarbamate in dichloromethane was prepared from chlorosulphonyl isocyanate and t-butanol (according to the procedure described by Dewynter in Tetrahedron Vol.49,1993 page 72). An aliquot (7.3 ml, 4.84 mmol) of this solution was added dropwise to a stirred solution of ethyl *N*-{4-[(acetylamino)methyl]phenyl}glycinate (1.1 g, 4.4 mmol) in dichloromethane (12 ml) containing triethylamine(533 mg, 5.3 mmol) under argon. The solution was stirred for 2 hours at ambient temperature and then diluted with dichloromethane (70 ml). The solution was washed sequentially with 0.1M HCl (2x20 ml), water (20 ml) and brine (20 ml), and then dried (MgSO4). The solution was evaporated under reduced pressure to give ethyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate (1.8 g); ^{1}H NMR ($CDCl_3$): 1.15(3H,t), 1.5(9H,s), 2.0(3H,s), 4.1(2H,m), 4.4(2H,d), 4.6(2H,s), 5.8(1H,br), 7.1(2H,d), 7.2(2H,d);

(iii) Ethyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate (1.8 g, 4.2 mmol) in 90% TFA/water (8 ml) was stirred for 1 hour at ambient temperature. The solution was evaporated to dryness under reduced pressure and then azeotroped twice with toluene to give ethyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-(aminosulphonyl)glycinate (1.38 g); ^{1}H NMR ($CDCl_3$): 1.2(3H,t), 2.0(3H,s), 4.2-4.5(8H,m), 6.1(1H,br), 7.3(2H,d), 7.4(2H,d).

Example 2

5-[4-(Cyanomethyl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

A solution of (4-aminophenyl)acetonitrile in DMF (3.0 ml, 0.72 M, 2.16 meq) was added to an aliquot of Polystyrene/Wang/Bromoacetate resin (300 mg, 0.9 meq/g, 0.27 meq) in a 4 ml reaction vial. The suspension was heated at 50 °C for 5 hours, allowed to cool to ambient temperature, drained, and washed serially with DMF (5 x 2 ml), THF (5 x 2 ml), and dichloromethane (5 x 2 ml). A solution of DIPEA in dichloromethane (2M;0.5 ml, 1.0 meq) was added. The reaction vial was cooled to –20 °C and a freshly prepared solution of 9*H*-

fluoren-9-ylmethyl chlorosulfonylcarbamate in dichloromethane (0.15 M; 2.9 ml, 0.44 meq) was added. The reaction vial was shaken for 2 hours at –20 °C and gradually (over 1 hour) warmed to 0 °C, followed by shaking at ambient temperature for 3 hours. The reaction vial was drained and washed serially with dichloromethane (3 x 2 ml), THF (3 x 2 ml, and DMF (3 x 2 ml). An 8% solution of 1,8-diazabicyclo[5.4.0]undec-7-ene in DMF (3 ml) was added to the reaction vial. The reaction vial was shaken for 75 hours at ambient temperature and the liquid contents collected. The remaining resin was washed with DMF (3 x 3 ml) and the washings combined with the initial collected liquid. The solvent was removed at reduced pressure to give the crude product. The crude product was treated with 2 ml of methanol and 0.3 meq of formic acid and subjected to reverse phase liquid chromatography. Like fractions were combined, concentrated by rotary evaporation, and dried at 50 °C, under vacuum, overnight to give the title compound (28.4 mg);

^{1}H NMR (DMSO-d_6): 9.48 (brs, 1H), 7.24 (d, 2H), 7.07 (d, 2H), 3.99 (d, 2H), 3.92 (d, 2H); m/z $(M-H)^-$ 250.

Polystyrene/Wang/Bromoacetate resin was obtained as follows:-

Diisopropylcarbodiimide (26.8 ml, 171 meq) was added in 5 aliquots to a solution/suspension of bromoacetic acid (47.5 g, 342 meq) at 0°C. The reaction mixture was stirred for 2.5 hours and solvent was removed by rotary evaporation at reduced pressure. The residue was taken up in dry, degassed DMF and added to a suspension of polystyrene/Wang linker resin (38.0 g, 0.9 meq/g, 34.2 meq) pre-swollen in DMF. 4-Dimethylaminopyridine (0.4 g, 3.42 meq) was then added to this solution/suspension. The entire mixture was stirred at ambient temperature for 24 hours, filtered through a coarse sintered glass funnel, and washed serially with 5 x 500 ml DMF, THF, dichloromethane, and DMF. The resin was subjected to the above reaction conditions a second time using only half the number of equivalents of the reagents (solvent volumes remained the same). After 24 hours, the resin mixture was filtered and washed serially with 5 x 500 ml each of DMF, THF, dichloromethane, and diethyl ether. The resin was dried under vacuum/N_2 for 1hour followed by high vacuum at 50 °C for 2 days. Quantitative incorporation of bromoacetate was showed by elemental analysis for bromine content.

Example 3

5-[4-(Acetamidomethyl)-2-methoxyphenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

A solution of 0.5 M sodium methoxide in methanol (1.34 ml,0.67 mmol) was added to a solution of methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}-*N*-(aminosulphonyl)glycinate (165 mg, 0.48 mmol) in methanol (3 ml) under argon and the solution was stirred at ambient temperature for 60 minutes. The mixture was quenched by the addition of 1M HCl (1 ml) and evaporated to remove the methanol. The residue was triturated with water, then isolated by filtration, washed with water then diethyl ether and dried under reduced pressure over phosphorus pentoxide to give the title product (123 mg) as a white solid:^{1}H NMR (DMSO-d6): 1.9 (3H,s), 3.8 (3H,s), 4.2 (2H,d), 4.4 (2H,s), 6.8 (1H,d), 7.0 (1H,s), 7.3 (1H,d), 8.3 (1H,br) : m/z 312 (M-H)

The starting material methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}-*N*-(aminosulphonyl)glycinate was obtained as follows:-

(i) A solution of 3-methoxy-4-nitrobenzyl alcohol (3.66 g, 20 mmol), triphenyl phosphine (5.24 g, 20 mmol) and phthalimide (2.94 g, 20 mmol) in dry THF (30 ml) under argon was cooled to 0 °C and a solution of di-*t*-butylazodicarboxylate (4.6 g, 20 mmol) in THF (10 ml) was then added dropwise over 30 minutes. The solution was allowed to warm up to ambient temperature and stirred overnight. The THF was removed by evaporation under reduced pressure and the residue crystallised from toluene, filtered, washed with toluene and dried under reduced pressure to give 2-(3-methoxy-4-nitrobenzyl)-1*H*-isoindole-1,3(2*H*)-dione as a solid (4.4 g). ^{1}H NMR (DMSO-d6): 3.9 (3H,s), 4.8 (2H,s), 7.0 (1H,d), 7.3 (1H,s), 7.8 (1H,d), 7.85-7.95 (4H,m);

(ii) 2-(3-Methoxy-4-nitrobenzyl)-1*H*-isoindole-1,3(2*H*)-dione (4.4 g, 14 mmol) was suspended in ethanol (40 ml) and hydrazine hydrate (1.034 ml, 21 mmol) was added. The resultant mixture was heated under reflux for 30 minutes and then evaporated to dryness, azeotroped with toluene and dried under reduced pressure over phosphorus pentoxide overnight. The mixture was suspended in dry pyridine (26 ml), cooled in an ice bath and treated with acetic anhydride (13.1 ml, 140 mmol). The resultant solution was stirred for 2 hrs at ambient temperature then poured into iced water (50 ml). The precipitate was removed by filtration and the filtrate was extracted with ethyl acetate (3 x 30 ml). The organic extracts were washed with water (20 ml), saturated brine (20 ml), dried over magnesium sulphate and evaporated to dryness. After trituration with diethyl ether, filtration and evaporation under

reduced pressure, *N*-(3-methoxy-4-nitrobenzyl)acetamide was obtained as a crystalline solid (2.86 g); ^{1}H NMR ($CDCl_3$): 2.1 (3H,s), 4.0 (3H,s), 4.5 (2H,d), 5.9 (1H,br), 6.9 (1H,d), 7.0 (1H,s), 7.8 (1H,d);

(iii) *N*-(3-methoxy-4-nitrobenzyl)acetamide (2.86 g, 12.75 mmol) was dissolved in ethanol (75 ml) and 10% Pd/C was added. The mixture was then hydrogenated for 2 hours. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was triturated with ether and filtered to give *N*-(4-amino-3-methoxybenzyl)acetamide (2.4 g); ^{1}H NMR ($CDCl_3$): 2.0 (3H,s), 3.9 (3H,s), 4.3 (2H,d), 5.6 (1H,br), 6.6-6.8 (3H,m);

(iv) Methyl bromoacetate (1.13 ml, 12 mmol) was added to a solution of *N*-(4-amino-3-methoxybenzyl)acetamide (2.4 g, 12.37 mmol) in DMF(25 ml) containing DIPEA (4.31 ml, 24.7 mmol), and the mixture was heated at 60°C overnight. After cooling to ambient temperature, the mixture was poured into ice water (50 ml) and extracted with ethyl acetate (3x50 ml). The combined ethyl acetate extracts were washed with water (30 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate/hexane to give methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}glycinate (1.5 g); ^{1}H NMR ($CDCl_3$): 2.0(3H,s), 3.7(3H,s), 3.8(3H,s), 3.9(2H,d), 4.3(2H,d), 4.8(1H,br), 5.6(1H,br), 6.4(1H,d), 6.7-6.8(2H,m);

(v) A 0.66 M solution of *tert*-butyl chlorosulfonylcarbamate in dichloromethane was prepared from chlorosulphonyl isocyanate and t-butanol (according to the procedure described by Dewynter in Tetrahedron Vol.49, 1993, page 72). An aliquot (9.4 ml, 6.2 mmol) of this solution was added dropwise to a stirred solution of methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}glycinate (1.5 g, 5.6 mmol) in dichloromethane (20 ml) containing DIPEA (1.26 ml, 5.3 mmol) under argon. The solution was stirred for 2 hours at ambient temperature and then diluted with dichloromethane (70 ml). The solution was washed sequentially with 0.1M HCl (2x20 ml), water (20 ml) and brine (20 ml), and then dried (MgSO4). The solution was evaporated under reduced pressure and the residue purified by column chromatography on silica eluting with dichloromethane then 4% methanol in dichloromethane to give methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate (471mg); ^{1}H NMR ($CDCl_3$): 1.5(9H,s), 2.0(3H,s), 3.7(3H,s), 3.9(3H,s), 4.4(2H,d), 4.6(2H,s), 5.9(1H,br), 6.8-6.9(2H,m), 7.6(1H,d);

(vi) Methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate (471 mg, 1.06 mmol) in 90% TFA/water (2 ml)

was stirred for 1 hour at ambient temperature. The solution was evaporated to dryness under reduced pressure and then azeotroped twice with toluene then purified by column chromatography on silica eluting with dichloromethane then 3% methanol in dichloromethane to give methyl *N*-{4-[(acetylamino)methyl]-2-methoxyphenyl}-*N*-(aminosulphonyl)glycinate (1.38 g); ^{1}H NMR ($CDCl_3$): 2.0(3H,s), 3.7(3H,s), 3.9(3H,s), 4.3(2H,s), 4.4(2H,d), 5.0(2H,s), 5.8(1H,br), 6.8(1H,d), 6.9(1H,s), 7.5(1H,d); m/z 345 (M + Na).

Example 4

5-[4-(Butanamidomethyl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 3, but starting with methyl *N*-(aminosulphonyl)- *N*-{4-[(butanoylamino)methyl]phenyl}glycinate, there was thus obtained the title product; ^{1}H NMR (DMSO-d6): 0.8 (3H,t), 1.5 (2H,q), 2.1 (2H,q), 4.2 (2H,d), 4.4 (2H,s), 7.1 (2H,dd), 7.2 (2H,dd), 8.2 (1H,br) : m/z 310 (M-H).

The starting material for Example 4 was obtained using analogous procedures to those described in Example 3, parts (iv) to (vi), starting from *N*-(4-aminobenzyl)butanamide instead of *N*-(4-amino-3-methoxybenzyl)acetamide. The following intermediates were obtained:- methyl *N*-{4-[(butanoylamino)methyl]phenyl}glycinate: ^{1}H NMR ($CDCl_3$): 1.0 (3H,t), 1.7 (2H,q), 2.2 (2H,t), 3.8 (3H,s), 3.9 (2H,s), 4.4 (3H,m), 5.6 (1H,br), 6.6 (2H,dd), 7.1 (2H,dd); methyl *N*-{4-[(butanoylamino)methyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate: ^{1}H NMR ($CDCl_3$): 1.0 (3H,t), 1.5 (9H,s), 1.7 (2H,q), 2.2 (2H,t), 3.7 (3H,s), 4.4 (2H,d), 4.6 (2H,s), 5.7 (1H,br), 7.3 (2H,dd), 7.4 (2H,dd); methyl *N*-(aminosulphonyl)- *N*-{4-[(butanoylamino)methyl]phenyl}glycinate: ^{1}H NMR ($CDCl_3$): 1.0 (3H,t), 1.7 (2H,q), 2.2 (2H,t), 3.8 (3H,s), 4.4 (4H,m), 5.1 (2H,s), 5.7 (1H,br), 7.3 (2H,dd), 7.4 (2H,dd).

N-(4-aminobenzyl)butanamide was obtained as follows:-

(i) 4-Nitrobenzylamine hydrochloride (1.89 g, 10 mmol) and DIPEA (3.82 ml, 22 mmol) in dichloromethane (20 ml) was cooled to 0 °C under argon and treated with butyryl chloride (1.06 g,11 mmol) and the solution stirred at ambient temperature for 2 hrs, then poured into water (30ml), separated and the organic layer washed with 2N citric acid (20 ml), sat. sodium bicarbonate solution (20 ml), water (20 ml) and brine (20 ml), dried with magnesium sulphate, filtered and evaporated to dryness to give 4-nitrobenzylbutanamide (1.89 g): ^{1}H NMR ($CDCl_3$): 1.0 (3H,t), 1.7 (2H,q), 2.2 (2H,t), 4.5 (2H,d), 5.9 (1H,br), 7.4 (2H,dd), 8.2(2H,dd)

(ii) 4-Nitrobenzylbutanamide (1.89 g) was dissolved in ethanol (50 ml), treated with 10% Pd/C and hydrogenated for 2 hrs. The catalyst was removed by filtration and the solution evaporated to dryness to give *N*-(4-aminobenzyl)butanamide (1.63g) as a white solid: ^{1}H NMR ($CDCl_3$): 0.9 (3H,t), 1.6 (2H,q), 2.2 (2H,t), 3.6 (2H,br), 4.2 (2H,d), 5.5 (1H,br), 6.7 (2H,dd), 7.0 (2H,dd)

Example 5

5-{4-[2-(Methylcarbamoyl)ethyl]phenyl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 3, but starting with methyl *N*-(aminosulphonyl)- *N*-{4-[3-(methylamino)-3-oxopropyl]phenyl}glycinate, there was thus obtained the title product; ^{1}H NMR (DMSO-d6): 2.3 (2H,t), 2.5 (3H,d), 2.7 (2H,t), 4.4 (2H,s), 7.1 (2H,dd), 7.2 (2H,dd), 7.7 (1H,br) : m/z 296 (M-H)

The starting material for Example 5 was obtained using analogous procedures to those described in Example 3, parts (iv) to (vi), starting from 3-(4-aminophenyl)-*N*-methylpropanamide. The following intermediates were obtained:-

methyl *N*-{4-[3-(methylamino)-3-oxopropyl]phenyl}glycinate : ^{1}H NMR ($CDCl_3$): 2.4 (2H,t), 2.8 (3H,d), 2.9 (2H,t), 3.7 (2H,s), 3.9 (3H,s), 4.2 (1H,br), 5.3 (1H,br), 6.6 (2H,dd), 7.0 (2H,dd);

methyl *N*-{4-[3-(methylamino)-3-oxopropyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate : ^{1}H NMR ($CDCl_3$): 1.5 (9H,s), 2.4 (2H,t), 2.8 (3H,d), 3.0 (2H,t), 3.7 (2H,s), 4.6 (2H,s), 5.4 (1H,b), 7.2 (2H,dd), 7.4 (2H,dd);

methyl *N*-(aminosulphonyl)- *N*-{4-[3-(methylamino)-3-oxopropyl]phenyl}glycinate: ^{1}H NMR ($CDCl_3$): 2.4 (2H,t), 2.7 (3H,d), 3.0 (2H,t), 3.8 (2H,s), 4.4 (2H,s), 5.1 (2H,s), 5.4 (1H,b), 7.2 (2H,dd), 7.4 (2H,dd).

Example 6

5-{4-[(5-Phenylpentanamido)methyl]phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 3, but starting with methyl *N*-(aminosulphonyl)-*N*-(4-{[(5-phenylpentanoyl)amino]methyl}phenyl)glycinate, there was thus obtained the title product; ^{1}H NMR (DMSO-d6): 1.5 (4H,m), 2.1 (2H,t), 2.6 (2H,t), 4.2 (2H,d), 4.4 (2H,s), 7.1–7.3 (9H,m), 8.2 (1H,br) : m/z 400 (M-H)

The starting material for Example 6 was obtained using analogous procedures to those described in Example 3, parts (iv) to (vi), starting from *N*-(4-aminobenzyl)-5-phenylpentanamide. The following intermediates were obtained:-

methyl *N*-(4-{[(5-phenylpentanoyl)amino]methyl}phenyl)glycinate: ^{1}H NMR ($CDCl_3$): 1.7 (4H,m), 2.2 (2H,t), 2.6 (2H,t), 3.8 (3H,s), 3.9 (2H,s), 4.4 (3H,m), 5.5 (1H,br), 6.6 (2H,dd), 7.1 (2H,dd), 7.1-7.3 (5H,m);

methyl *N*-(4-{[(5-phenylpentanoyl)amino]methyl}phenyl)-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonyl}glycinate: ^{1}H NMR ($CDCl_3$): 1.5 (9H,s), 1.7 (4H,m), 2.2 (2H,t), 2.6 (2H,t), 3.8 (3H,s), 4.4 (2H,d), 4.6 (2H,s), 5.7 (1H,br), 7.2 (3H,m), 7.3 (4H,m), 7.4 (2H,d): m/z 532 (M-H);

methyl *N*-(aminosulphonyl)-*N*-(4-{[(5-phenylpentanoyl)amino]methyl}phenyl)glycinate: ^{1}H NMR ($CDCl_3$): 1.7 (4H,m), 2.2 (2H,t), 2.6 (2H,t), 3.8 (3H,s), 4.4 (4H,m), 5.1 (2H,s), 5.7 (1H,br), 7.1 (4H,m), 7.3 (3H,m), 7.4 (2H,d): m/z 456 (M+Na).

N-(4-aminobenzyl)-5-phenylpentanamide [^{1}H NMR ($CDCl_3$): 1.6 (4H,m), 2.2 (2H,t), 2.6 (2H,t), 4.3 (2H,d), 5.5 (1H,br), 6.6 (2H,dd), 7.0 (2H,dd), 7.1 (3H,m), 7.2 (2H,t)] was obtained using analogous procedures to those described for the preparation of *N*-(4-aminobenzyl)butanamide in Example 4, but using 5-phenylpentanoyl chloride in place of butyryl chloride. The following intermediate was obtained:-

N-(4-nitrobenzyl)-5-phenylpentanamide: ^{1}H NMR ($CDCl_3$): 1.7 (4H,m), 2.2 (2H,t), 2.6 (2H,t), 4.5 (2H,d), 5.8 (1H,br), 6.6 (2H,dd), 7.0 (2H,dd), 7.1 (3H,m), 7.2 (2H,t)), 7.4 (2H,dd), 8.1 (2H,dd),

Example 7

5-[4-(Acetamidomethyl)phenyl]-4-methyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 3, but starting with methyl *N*-(aminosulphonyl)-*N*-{4-[(acetylamino)methyl]phenyl}alaninate, there was thus obtained the title product; ^{1}H NMR (DMSO-d6): 1.2 (3H,d), 1.8 (3H,s), 4.0 (1H,br), 4.2 (2H,d), 4.3 (1H,q), 7.1 (2H,dd), 7.2 (2H,dd), 8.2 (1H,br) : m/z 296 (M-H).

The starting material for Example 7 was obtained using analogous procedures to those described in Example 3, parts (iv) to (vi), starting from *N*-(4-aminobenzyl)acetamide and methyl 2-bromopropionate. The following intermediates were obtained:-

methyl *N*-{4-[(acetylamino)methyl]phenyl}alaninate : ^{1}H NMR ($CDCl_3$): 1.3 (3H,d), 1.9 (3H,s), 3.7 (3H,s), 4.2 (2H,m), 4.3 (2H,d), 5.6 (1H,br), 6.5 (2H,dd), 7.1 (2H,dd);

methyl *N*-{4-[(acetylamino)methyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulphonylalaninate: ^{1}H NMR ($CDCl_3$): 1.3 (3H,d), 1.5 (9H,s), 2.1 (3H,s), 3.8 (3H,s), 4.4 (2H,d), 5.2 (1H,q), 5.9(1H,br), 7.3 (2H,dd), 7.4 (2H,dd);

methyl *N*-(aminosulphonyl)-*N*-{4-[(acetylamino)methyl]phenyl}alaninate: ^{1}H NMR ($CDCl_3$): 1.3 (3H,d), 2.1 (3H,s), 3.8 (5H,m), 4.5 (2H,d), 5.0 (1H,q), 6.5 (1H,br), 7.1 (2H,dd), 7.2 (2H,dd), 8.2 (1H,br).

Example 8

5-[4-(2-Acetamidoethyl)phenyl]-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Using an analogous procedure to that described in Example 3, but starting with methyl *N*-{4-[2-(acetylamino)ethyl]phenyl}-*N*-(aminosulfonyl)glycinate, there was thus obtained the title product; ^{1}H NMR (DMSO-d6) 1.8 (3H, s), 2.6 (2H, t), 3.2 (2H, q), 4.3 (2H, s), 5.4 (1H, br), 7.1 (2H, d), 7.2 (2H, d), 7.9 (1H, t): m/z 296 $[M-H]^-$

The starting material for Example 8 was obtained using analogous procedures to those described in Example 3, parts (iv) to (vi), starting from *N*-[2-(4-aminophenyl)ethyl]acetamide (itself obtained as described in Tetrahedron Lett, 1982, 23, 1159-60). The following intermediates were obtained:-

methyl *N*-{4-[2-(acetylamino)ethyl]phenyl}glycinate

^{1}H NMR ($CDCl_3$) 1.9 (3H, s), 2.7 (2H, t), 3.5 (2H, q), 3.8 (3H, s), 3.9 (2H, s), 4.2 (1H, s), 5.4 (1H, s), 6.6 (2H, d), 7.0 (2H, d): m/z 251 $[M+H]^+$;

methyl *N*-{4-[2-(acetylamino)ethyl]phenyl}-*N*-{[(*tert*-butoxycarbonyl)amino]sulfonyl} glycinate

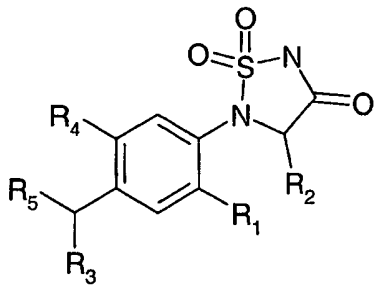
^{1}H NMR (DMSO-d6) 1.5 (9H, s), 1.8 (3H, s), 2.7 (2H, t), 3.3 (2H, q), 3.6 (3H, s), 4.6 (2H, s), 7.3 (4H, m), 8.0 (1H, s), 11.3 (1H, s): m/z 428 $[M-H]^-$;

methyl *N*-{4-[2-(acetylamino)ethyl]phenyl}-*N*-(aminosulfonyl)glycinate

^{1}H NMR ($CDCl_3$) 1.9 (3H, s), 2.8 (2H, t), 3.5 (2H, q), 3.8 (3H, s), 4.4 (2H, s), 5.1 (2H, s), 5.5 (1H, s), 7.2 (2H, d), 7.4 (2H, d): m/z 352 $[M+Na]^+$.

Claims

1. A compound of formula (I):



(I)

wherein

R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;

or R_1 is a group of the formula $-Z-(CHR_6)_m-X-NR_7R_8$ wherein

m is 1, 2 or 3;

R_6 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $–S(O)_2$-; and R_7 and R_8 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_7 and R_8 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_7 is hydrogen, (1-6C)alkyl or aryl, and R_8 is $–COR_9$ or SO_2R_9 wherein R_9 is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is selected from H, (1-6C)alkyl, halogeno, halogeno(1-6C)alkyl and (1-6C)alkoxy;

R_3 is $-NHR_{10}$ wherein R_{10} is $–C(O)R_{11}$, and R_{11} is $-(CHR_{12})_n-R_{13}$; or R_3 is $-(CHR_{14})_p-R_{15}$ wherein R_{14} is hydrogen or (1-6C)alkyl and

R_{15} is (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, cyano, carbamoyl or $-CONH-(CHR_{12})_n-R_{13}$; or R_{15} is $-NHR_{10}$ wherein R_{10} is as defined above; or R_{15} is $–(CHR_{16})_q-CONH-(CHR_{12})_n-R_{13}$ wherein R_{16} is amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, carbamoyl, $-CONH-(CHR_{12})_n-R_{13}$ or $-NHR_{10}$ wherein R_{10} is as defined above; and wherein n is the integer 1, 2 or 3; p is zero or the integer 1,2 or 3; q is the integer 1, 2 or 3; and R_{12}, R_{13} and R_{16} are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkyl, hydroxy, hydroxy(1-6C)alkyl, (1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkyl, (1-6C)alkylsulfonyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkylsulfinyl, (1-6C)alkylsulfinyl(1-6C)alkyl, aryl, aryloxy, aryl(1-6C)alkyl, heteroaryl, heteroaryloxy, heteroaryl(1-6C)alkyl, amino, amino(1-6C)alkyl, carboxy, carboxy(1-4C)alkyl, carbamoyl, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino, (2-6C)alkanoylamino(1-6C)alkyl, sulfamoyl and sulfamoyl(1-6C)alkyl; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_4 is hydrogen, (1-6C)alkyl, aryl or heteroaryl;

R_5 is hydrogen or (1-6C)alkyl;

and wherein any aryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,

N,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;
or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (I) as claimed in Claim 1, wherein:
R_1 is hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, halogeno, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, (1-6C)alkoxy(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, (1-6C)alkylthio(1-6C)alkyl, arylthio(1-6C)alkyl, heteroarylthio(1-6C)alkyl, (1-6)alkylsulfinyl(1-6C)alkyl, arylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, arylsulfonyl(1-6C)alkyl, carbamoyl(1-6C)alkoxy, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, hydroxy(1-6C)alkyl, amino(1-6C)alkyl, carboxy(1-6C)alkyl, sulfamoyl(1-6C)alkyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (2-8C)alkenyl, (2-8C)alkynyl, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino;
or R_1 is a group of the formula $-Z-(CHR_6)_m-X-NR_7R_8$ wherein

m is 1, 2 or 3;

R_6 is hydrogen, (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl, hydroxy or (1-6C)alkoxy;

X is –C(O)-, -S(O)- or $–S(O)_2$-; and R_7 and R_8 are independently selected from hydrogen, (1-6C)alkyl, aryl and heteroaryl; or R_7 and R_8 together with the nitrogen atom to which they are attached form a heterocyclic ring; or X is a covalent bond, R_7 is hydrogen, (1-6C)alkyl or aryl, and R_8 is $–COR_9$ or SO_2R_9 wherein R_9 is (1-6C)alkyl, aryl, heteroaryl, aryl(1-6C)alkyl or heteroaryl(1-6C)alkyl; and

Z is a covalent bond, O or S; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_2 is H or (1-6C)alkyl;

R_3 is $-NHR_{10}$ wherein R_{10} is $–C(O)R_{11}$ or $–S(O)_2R_{11}$, and R_{11} is $-(CHR_{12})_n-R_{13}$; or R_3 is $-(CHR_{14})_p-R_{15}$ wherein R_{14} is hydrogen or (1-6C)alkyl and

R_{15} is (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, cyano, carbamoyl or $-CONH-(CHR_{12})_n-R_{13}$; or R_{15} is $-NHR_{10}$ wherein R_{10} is as defined above; or R_{15} is $–(CHR_{16})_q-CONH-(CHR_{12})_n-R_{13}$ wherein R_{16} is amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, morpholino, thiomorpholino, carbamoyl, $-CONH-(CHR_{12})_n-R_{13}$ or $-NHR_{10}$ wherein R_{10} is as defined above; and wherein n is the integer 1, 2 or 3; p is zero or the integer 1,2 or 3; q is the integer 1, 2 or 3; and R_{12}, R_{13} and R_{16} are independently selected from hydrogen, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkyl, hydroxy, hydroxy(1-6C)alkyl, (1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkyl, (1-6C)alkylsulfonyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkylsulfinyl, (1-6C)alkylsulfinyl(1-6C)alkyl, aryl, aryloxy, aryl(1-6C)alkyl, heteroaryl, heteroaryloxy, heteroaryl(1-6C)alkyl, amino, amino(1-6C)alkyl, carboxy, carboxy(1-4C)alkyl, carbamoyl, carbamoyl(1-6C)alkyl, (2-6C)alkanoylamino, (2-6C)alkanoylamino(1-6C)alkyl, sulfamoyl and sulfamoyl(1-6C)alkyl; with the proviso that no two heteroatoms are attached through single bonds to the same carbon atom;

R_4 is hydrogen, (1-6C)alkyl, aryl or heteroaryl;

R_5 is hydrogen or (1-6C)alkyl;

and wherein any aryl or heteroaryl group within or part of the definition of R_1, R_3 or R_4 is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-

6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N*,*N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N*,*N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, (1-6C)alkoxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(1-6C)alkyl, aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, aryloxy(1-6C)alkyl, heteroaryloxy(1-6C)alkyl, aryl(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, aryloxy and heteroaryloxy, and wherein an aryl or heteroaryl moiety of said last ten groups is unsubstituted or bears 1, 2 or 3 substituents, which may be the same or different; or two adjacent carbons of said aryl or heteroaryl group may be linked by a divalent radical of formula $-O(CH_2)_{1-4}O-$;
or a pharmaceutically acceptable salt thereof.

3. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 1, wherein R_1 is selected from (1-6C)alkoxy, (1-6C)alkylthio, halogeno(1-6C)alkoxy, halogeno(1-6C)alkylthio, hydroxy(1-6C)alkoxy, dihydroxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, aryloxy, aryl(1-6C)alkoxy, aryloxy(1-6C)alkoxy, heteroaryl(1-6C)alkoxy, heteroaryloxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkylthio, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkylthio, aryloxy(1-6C)alkylthio, heteroaryl(1-6C)alkylthio, heteroaryloxy(1-6C)alkylthio, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy.

4. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 1, wherein R_1 is selected from (1-6C)alkoxy, hydroxy-(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkylthio(1-6C)alkoxy, (1-6C)alkylsulfinyl(1-6C)alkoxy, (1-6C)alkylsulfonyl(1-6C)alkoxy, aryl(1-6C)alkoxy, fluoro(1-6C)alkoxy, carbamoyl(1-6C)alkoxy, (2-6C)alkanoylamino(1-6C)alkoxy, (1-6C)alkoxy-(1-6C)alkyl, aryloxy(1-6C)alkyl, (1-6C)alkylsulfinyl(1-6C)alkyl, (1-6C)alkylsulfonyl(1-6C)alkyl, (1-6C)alkanoylamino(1-6C)alkyl and carbamoyl(1-6C)alkyl;
R_2, R_4 and R_5 are each hydrogen; R_3 is $-(CHR_{14})_p-NH-CO-R_{11}$ wherein p is 0 or 1 and R_{14} is hydrogen.

5. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 4, wherein R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} and R_{13} are independently selected from hydrogen and (1-4C)alkyl and n is 1, 2 or 3.

6. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 4, wherein R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} is hydrogen, R_{13} is aryl or aryl(1-6C)alkyl, and n is 1, 2 or 3.

7. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 4, wherein R_{11} is $-(CHR_{12})_n-R_{13}$ in which R_{12} and R_{13} are independently selected from hydrogen and (1-4C)alkyl and n is 1, 2 or 3

8. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims wherein R_1 is (1-6C)alkoxy.

9. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims wherein R_1 is (1-4C)alkoxy.

10. A compound of the formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims wherein R_1 is methoxy.

11. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

12. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 for use in a method of prophylactic or therapeutic treatment of diabetes mellitus.in a warm-blooded animal, such as man.

13. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 for use as a medicament.

14. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 for use as a medicament for producing a PTP1B inhibitory effect in a warm-blooded mammal, such as man.

15. The use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in the manufacture of a medicament for use in the production of a PTP1B inhibitory effect in a warm-blooded animal, such as man.

16. The use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 in the manufacture of a medicament for use in the treatment of diabetes mellitus.

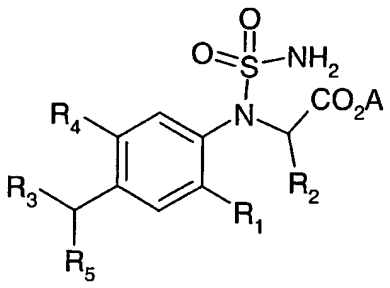
17. A method for producing a PTP1B inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1.

18. A method for treating diabetes mellitus in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1.

19. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 as a pharmacological tool in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of PTP1B in laboratory animals.

20. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of Claims 1 to 10 which process comprises of:

(a) cyclisation of a compound of formula (II):



(II)

wherein A is a (1-6C)alkyl, aryl or aryl(1-6C)alkyl group, for example methyl, ethyl, phenyl or benzyl, or A is a linking group to a solid phase resin, for example polystyrene/Wang resin;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Interne Application No
PCT/GB 03/05120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D285/10 A61K31/433

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/40017 A (NOVONORDISK AS) 30 October 1997 (1997-10-30) cited in the application the whole document	1-20
A	WO 99/46268 A (NOVONORDISK AS ; ONTOGEN CORP (US)) 16 September 1999 (1999-09-16) the whole document	1-20
A	WO 02/11722 A (AVENTIS PHARMA GMBH) 14 February 2002 (2002-02-14) the whole document	1-20
P,X	WO 03/082841 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); COPPOLA GARY MARK (US); DAVIE) 9 October 2003 (2003-10-09) the whole document	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 2004	08/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Von Daacke, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int onal application No.
PCT/GB 03/05120

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

mation on patent family members

Interna... Application No
PCT/GB 03/05120

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